

Clinical Investigation

Humid Air Increases Airway Resistance in Asthmatic Subjects

MOIRA L. AITKEN, MB, MRCP; JOHN J. MARINI, MD; and BRUCE H. CULVER, MD, Seattle

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Eight persons with asthma were exposed to seven air conditions varying in temperature (37°C to 49°C [98.6°F to 120.2°F]) and water content (44 mg H₂O per liter to 79 mg H₂O per liter). Normocapnic hyperventilation for three minutes at 40% maximal voluntary ventilation was carried out for each condition. A constant-volume body plethysmograph measured the functional residual capacity and specific airway conductance (SG_{aw}), followed by two forced expiratory maneuvers. Measurements were taken before and 1, 5, 10, and 20 minutes after each challenge. Air conditions with 100% relative humidity caused a fall in the SG_{aw} that was maximal in 1 minute. Air conditions at 100% relative humidity caused a greater fall in both the forced expiratory volume in 1 second (FEV₁) (P < .05) and the SG_{aw} (P < .005) than did conditions of the same temperature but less water content. At 44°C and 100% relative humidity, the mean percent change in FEV₁ and SG_{aw} was -2% and -40%, respectively, at 1 minute after challenge. Of the conditions examined, the optimal temperature was 44°C, and we speculate that the optimal water content is less than 44 mg H₂O per liter. Inhaled water concentrations exceeding 44 mg H₂O per liter should probably not be used in patients with asthma.

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Bronchoconstriction often occurs when persons with asthma exercise or do eucapnic hyperventilation when breathing cold air.¹⁻⁸ Usually little bronchoconstriction occurs when asthmatic subjects breathe air of 37°C (98.6°F), 100% relative humidity—44 mg H₂O per liter water content.³ We previously showed that bronchoconstriction also occurs when persons with asthma hyperventilate while breathing heated air at 50°C (122°F), 100% relative humidity (83 mg H₂O per liter).⁹

Inhaling nebulized distilled water produces bronchospasm due to a hypo-osmolar challenge.¹⁰ Because warm humid air would be expected to deposit water on the bronchial mucosa, we questioned whether the bronchospasm we had observed with breathing at 50°C, 100% relative humidity was induced by hypo-osmolality or by an additive effect of water and temperature. We therefore examined the airway response in asthmatic subjects to inhaling hot humid air of increasing temperature with a constant water content—selectively increasing heat delivery—and then increasing both temperature and water content, thereby increasing the heat delivery and water content simultaneously.

Methods

Subjects

We studied eight treated patients with asthma: six men, two women, aged 25.8 ± 7.3 years (mean ± standard deviation; range, 19 to 41 years).

Baseline spirometry showed a forced expiratory volume in one second (FEV₁) of 3.2 ± 0.8 liters, range, 2.07 liters to 4.24 liters, percent of predicted, 87% ± 23%; a forced vital capacity (FVC) of 4.8 ± 1.1 liters, range, 3.18 liters to 6.00 liters; and a forced expiratory flow rate measured between 25% and 75% of the FVC (FEF_{25-75%}) of 2.3 ± 1.7 liters per second, range, 1.26 liters per second to 3.24 liters per second. The FEV₁ was 66.6% ± 5.3% of the FVC. All gave informed consent for a protocol approved by the committee of the University of Washington School of Medicine for the Protection of Human Subjects. Each showed a significant response to 20 breaths of a nebulized, undiluted solution of 1% isoetharine¹¹ in one or more of these spirometric indices: FVC, FEV₁, or FEF_{25-75%}. A questionnaire concerning medical history, current medications, smoking history, and exercise symptoms was administered. All subjects were nonsmokers and had had intermittent episodes of cough and wheeze for at least 15 years. All experienced exercise-induced asthma. The last exacerbation of disease was more than four months previously. Five subjects had been using a theophylline preparation, six an inhaled β-agonist, and one inhaled steroids.

Apparatus

A machine specifically designed to provide large quantities of air adjusted to the temperature and humidity condi-

From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine and the Pacific Medical Center, Seattle (Drs Aitken and Culver), and the Department of Respiratory Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee (Dr Marini).

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Reprint requests to Moira L. Aitken, MD, MRCP, Pacific Medical Center, 1200 12th Ave S, Room 10402, Seattle, WA 98144.

ABBREVIATIONS USED IN TEXT

FEF_{25-75%} = forced expiratory flow rate between 25% and 75% of total vital capacity
 FEV₁ = forced expiratory volume in 1 second
 FRC = functional residual capacity
 FVC = forced vital capacity
 MVV = maximal voluntary ventilation
 SG_{aw} = specific airway conductance
 ΔSG_{aw} = change in specific airway conductance

tions required was connected by a valved manifold to a constant-volume plethysmograph (Figure 1). This assembly allowed the specific airway conductance (SG_{aw}) and the functional residual capacity (FRC) to be determined within seconds of terminating each hyperventilation challenge. Details of design are provided in a previous communication.⁹ Temperature and humidity of the inspire were measured 10 cm upstream from the lips. Temperature was measured with a mercury thermometer. Humidity was measured using a hygromechanical strip sensor (model #8501 A, Hygrometrix Inc, Oakland, Calif). Carbon dioxide was added 150 cm upstream. Normocapnic hyperventilation of conditioned air was achieved using a modification of a method described previously.⁹ During hyperventilation, the manifold was continuously evacuated at a predetermined rate by a controlled vacuum. A 13-liter spirometer joined to a side port of the expiratory line served as a reservoir to buffer transient deviations from the desired rate of ventilation. A variable resistor modulated by the spirometer bell provided the signal to a meter that cued a patient to the desired level of ventilation. The carbon dioxide tension of the exhaled air was sensed at the mouthpiece by the probe of a rapidly responding gas analyzer (LB-2, Beckman Instruments Inc, Schiller Park, Ill). During measurements of the SG_{aw} and the FRC, the plethysmograph was isolated from the conducting segments of the manifold by closing solenoid shutter valves at the points of entry and exit.

Protocol

Normocapnic hyperventilation trials were performed with each of the seven air conditions shown in Table 1 and

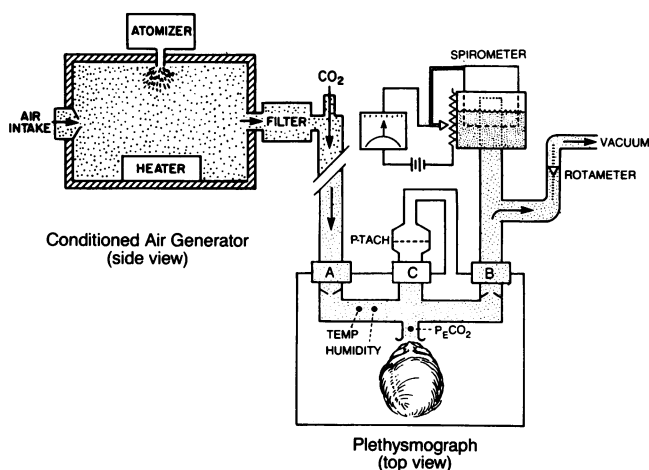


Figure 1.—The figure shows the testing apparatus used. During each hyperventilation trial, a one-way flow of conditioned air enters and exits the plethysmograph at a predetermined rate through heavily insulated tubing. By adjusting shutters A, B, and C, the plethysmograph can be made functional within seconds of discontinuing the challenge. P_ECO₂ = partial expiratory carbon dioxide tension, P-TACH = pneumotachygraph, TEMP = temperature

TABLE 1.—Temperature and Humidity of 7 Air Conditions Used to Test Airway Response in Persons With Asthma

| Air Condition | Temperature, °C (°F) | Absolute Water Content, mg/liter ⁻¹ |
|---------------|----------------------|--|
| 1 | 37 (98.6) | 44 |
| 2 | 40 (104.0) | 44 |
| 3 | 44 (111.2) | 44 |
| 4 | 49 (120.2) | 44 |
| 5 | 40 | 52 |
| 6 | 44 | 63 |
| 7 | 49 | 79 |

Figure 2. A hyperventilation target of 40% of maximal voluntary ventilation (MVV) was used for each exposure. The MVV was estimated as 35 times the forced expiratory volume in one second, measured on the first day of the study. Testing was conducted over one to five days, depending on the response. If the specific airway conductance decreased more than 30% after challenge, no further testing was done that day. Because seven different air conditions were tested, all subjects had more than one challenge on some days.

The subjects were trained to pant appropriately for measurements made with the body plethysmograph.^{12,13} Before each challenge, three to five baseline determinations of functional residual capacity and specific airway conductance were made and two forced expiratory spirometric maneuvers were done with the subjects breathing ambient air. Conditioned air was then drawn by vacuum through the manifold, and temperature and relative humidity allowed to stabilize to the specific condition under study. With nose clips placed, each person then hyperventilated normocapnicly from the mouthpiece for three minutes. The partial pressure of carbon dioxide was maintained at the initial resting level by adding CO₂ to the inspire. After completing the challenge, the

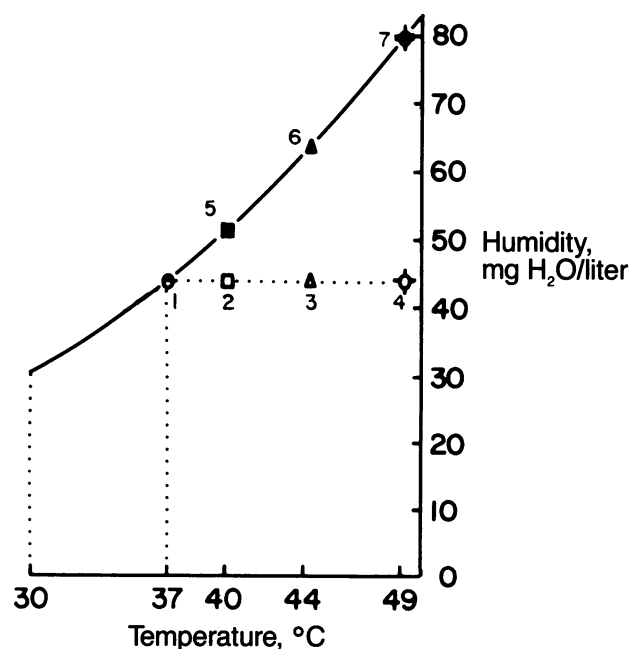


Figure 2.—The graph shows the temperature and absolute humidities of seven air conditions tested. Conditions 1 through 4 all have water contents of 44 mg H₂O per liter with temperatures of 37°C, 40°C, 44°C, and 49°C (98.6°F, 104°F, 111°F, and 120°F), respectively. Conditions 5 through 7 have temperatures corresponding to conditions 2 through 4—that is, 40°C, 44°C, and 49°C—but have 100% relative humidity.

subject briefly (10 to 15 seconds) removed the mouthpiece to clear oropharyngeal secretions. Three to five measurements of the FRC and SG_{aw} were then done within 90 seconds, followed by two forced expiratory maneuvers. Measurements were repeated between the 5th and 6th, the 10th and 11th, and 20th and 21st minutes following the hyperventilation challenge. Following the hyperventilation challenge, patients breathed ambient air during all testing.

Statistical Methods

The mean of each set of three to five SG_{aw} and FRC determinations was used in the statistical analysis. The better of each pair of FVC, FEV_1 , and $FEF_{25-75\%}$ measurements was used. The influence of time, humidity, and temperature on changes in the SG_{aw} , FRC, FVC, FEV_1 , and $FEF_{25-75\%}$ was determined using a three-way analysis of variance with individual comparisons made by contrasts.¹⁴ The Student's *t* test for paired variates was applied to examine changes in the SG_{aw} , FRC, FVC, FEV_1 , and $FEF_{25-75\%}$ at the same temperature but varying humidity. Linear regression was used to correlate the change in the SG_{aw} (ΔSG_{aw}) at one minute and the humidity.

Results

With the exception of condition 3 (44°C [111°F], 44 mg H_2O per liter), all conditions caused an abrupt, immediate fall in the SG_{aw} —that is, seen at one minute. At all times of testing, there was no difference seen in the SG_{aw} with conditions of the same water content (44 mg H_2O per liter) but varying temperatures ($P > .05$). When both temperature and humidity were increased together, however, there was a fall in the SG_{aw} that was pronounced at the time of first testing, with recovery thereafter (Figure 3).

Small changes were noted in the spirometric indices (Table 2 and Figure 3). A small bronchodilatory effect was seen with condition 3 (44°C, 44 mg H_2O per liter) in the FEV_1 (Figure 3). In comparing conditions of the same temperature but different water content (100% saturated or partially saturated—44 mg H_2O per liter), conditions at 44°C (conditions 3 and 6) were significantly different, both in the FEV_1 ($P < .05$) and the SG_{aw} ($P < .005$; Figure 3).

With conditions with 100% relative humidity—that is, conditions 5, 6, and 7—the maximal fall in the SG_{aw} was seen at the one-minute observation. It appears that there is a linear correlation between the mean ΔSG_{aw} observed at one minute and the humidity (Figure 4; $r = .09$, $P < .01$).

Discussion

These results suggest that the water content above 44 mg per liter—that is, fully saturated air above body temperature—may be detrimental to patients with asthma. A beneficial effect is seen when the temperature is raised slightly, to 44°C, but the water content remains that of the body temperature fully saturated (44 mg H_2O per liter). A progressively detrimental effect is observed as the water content is increased.

The disproportionate response in the SG_{aw} versus spirometric indices suggests that the proximal airways may have experienced the bulk of the detrimental effect. Because spirometry was always done after the initial SG_{aw} measurement, it is possible that the apparently disproportionate effect is partially explained by a waning transient bronchoconstriction. Another possibility is that the deep breaths associated

with doing spirometry may partially reverse the observed bronchospasm. The SG_{aw} and spirometric data, however, also differed regarding the time course of response in that the maximal decrease in the SG_{aw} occurred at 1 minute whereas the detrimental spirographic effects persisted unchanged throughout the 20-minute period of observation.

Because water was progressively added to the inspire, a linear relationship of the ΔSG_{aw} against increasing the water content of the inspire was seen at the time of the first testing. If one extrapolates that linear relationship, the point at which the ΔSG_{aw} intersects the X axis would be the abso-

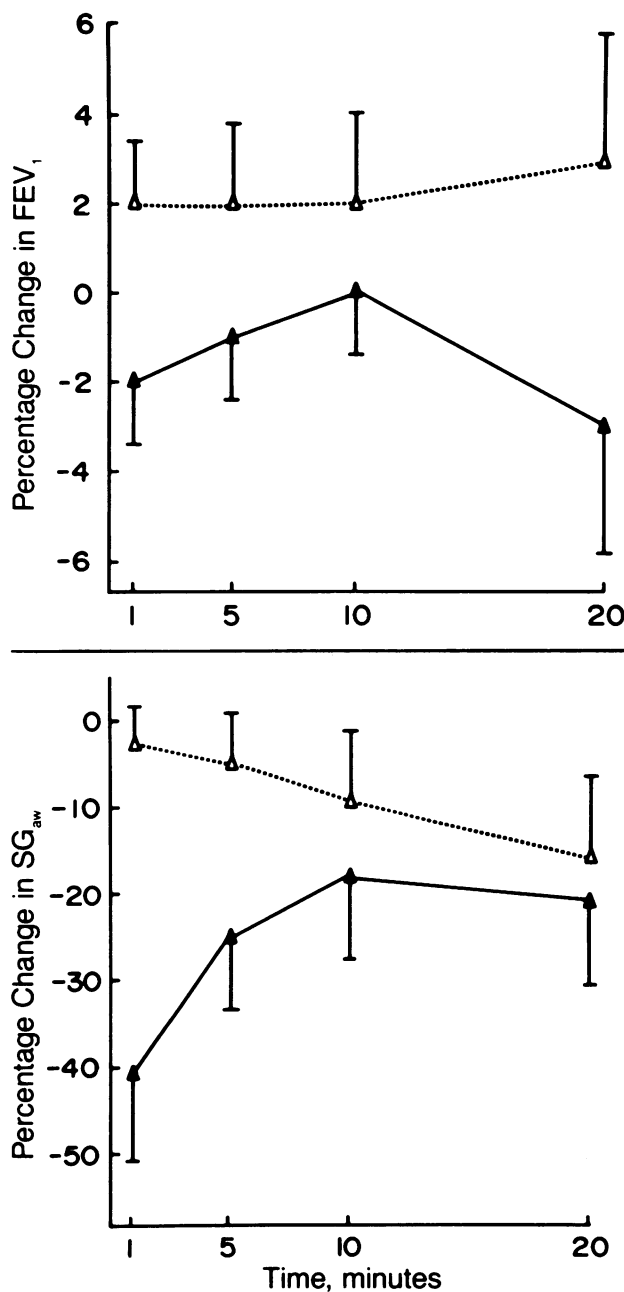


Figure 3.—The graphs show the mean percentage changes in (top) the forced expiratory volume in 1 second (FEV_1) and (bottom) the specific airway conductance (SG_{aw}) from baseline at 1, 5, 10, and 20 minutes after hyperventilation challenge in 8 subjects with asthma. Δ = condition 3 (44°C [111°F], 44 mg H_2O per liter); \bullet = condition 6 (44°C, 100% relative humidity). At all times of testing, condition 3 differs from condition 6 in both the FEV_1 and the SG_{aw} .

TABLE 2.—Change in Pulmonary Function Indices After Inhalation of 7 Different Air Conditions Over Time*

| Air Condition† | ΔFVC , liters—Minutes | | | | $\Delta FEF_{25-75\%}$, liters/s—Minutes | | | | ΔFRC , liters—Minutes | | | |
|----------------|-------------------------------|------|------|------|---|------|-------|-------|-------------------------------|------|------|------|
| | 1 | 5 | 10 | 20 | 1 | 5 | 10 | 20 | 1 | 5 | 10 | 20 |
| 1 | -1±1 | 0±1 | -2±1 | -2±1 | +1±5 | -2±5 | -3±5 | -2±7 | +1±2 | -2±2 | -2±2 | -4±3 |
| 2 | +1±1 | +1±1 | +1±1 | 0±1 | -5±2 | -8±4 | -6±4 | -12±7 | -1±3 | +2±3 | +1±1 | +1±1 |
| 3 | +2±1 | +1±1 | +1±1 | +1±1 | +3±4 | +5±6 | +2±4 | +6±7 | -2±2 | -4±2 | -3±2 | -4±3 |
| 4 | -2±1 | 0±1 | -3±2 | -3±1 | -1±4 | -4±5 | -10±5 | -5±7 | -1±2 | -3±2 | -2±2 | -4±2 |
| 5 | 0±1 | 0±1 | 0±1 | -2±1 | -9±2 | -1±4 | -8±5 | -7±5 | +1±3 | -4±1 | 0±3 | -3±3 |
| 6 | +1±1 | +1±1 | 0±1 | -2±1 | -8±3 | -5±3 | 0±3 | -6±6 | +5±3 | +1±3 | -2±2 | -1±2 |
| 7 | 0±1 | -1±1 | 0±1 | +1±1 | -9±2 | -4±4 | +3±3 | -7±3 | +5±3 | -3±3 | -1±4 | -6±4 |

FEF_{25-75%}=forced expiratory flow rate measured between 25% and 75% of total vital capacity, FRC=functional residual capacity, FVC=forced vital capacity

*Mean ± standard error of the mean.
†See Table 1 for description of air conditions.

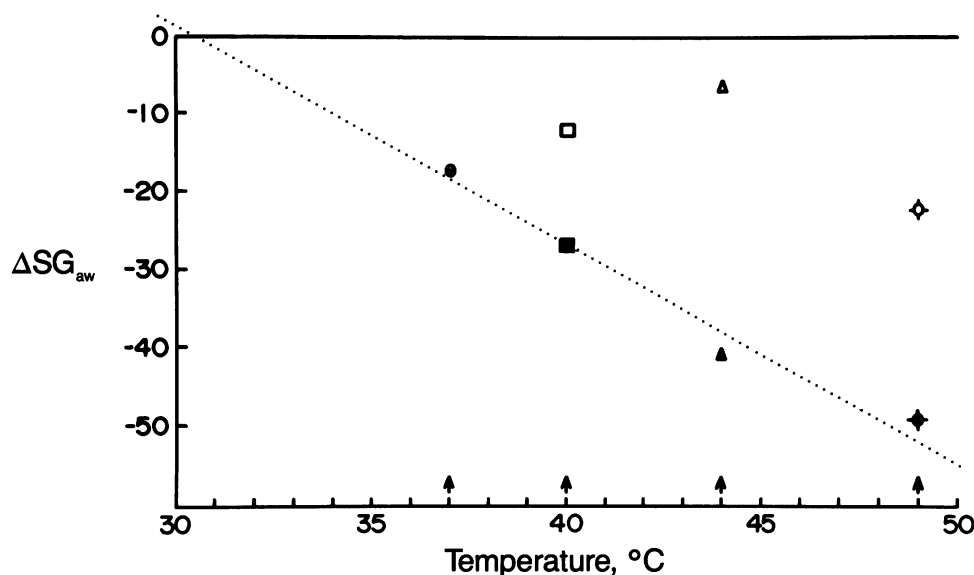


Figure 4.—The graph shows the mean change in the specific airway conductance (ΔSG_{aw}) of 8 subjects with asthma at 1 minute after a hyperventilation challenge. The solid symbols indicate fully saturated conditions (see Figure 2 for complete explanation). The dotted line is an extrapolation of the fully saturated data points through the baseline SG_{aw} . Where these lines intersect—that is, 30.3°C (86.5°F)—represents a water content of 30 mg H_2O per liter at 100% relative humidity.

lute water content of 30 mg H_2O per liter, which is the 100% relative humidity of 30.3°C. We speculate that inspired air carrying 30 mg H_2O per liter would have no detrimental effect. Moreover, the optimal temperature by our present study is about 44°C. When a person with asthma inhales air of 44°C and 30 mg H_2O per liter, a bronchodilator effect may occur.

We previously showed a mild (10%) improvement in airway conductance when the temperature and heat content of the inspire were increased in isocapnically hyperventilating normal subjects.⁹ More pronounced bronchodilation might have occurred if the inhaled water content had been less than 44 mg H_2O per liter. Moreover, in vitro, bronchial smooth muscle relaxes when examined in an isotonic solution of 40°C.¹⁵

Although care was taken to filter preformed droplets from the conditioned airstream, it is possible that small water particles form in the upper airway as the hot humid air is cooled to body temperatures. These particles may constitute an irritant stimulus acting on vagal receptors,¹⁵⁻¹⁷ possibly explaining the maximal immediate detrimental effect in the ΔSG_{aw} .

An alternative mechanism by which the humid conditions may cause bronchospasm is by water depositing on the respiratory mucosa, rendering it hypo-osmolar. When cold air is breathed, the respiratory tract becomes hyperosmolar as the cold dry air evaporates water from the mucosa¹⁸ and maximal bronchospasm is observed after several minutes of hy-

perventilation.¹⁹ Thus, the time course of hypo-osmolar conditions appears to be different from the response observed in this study. Supersaturated conditions may deposit water proximally, and hypo-osmolality is seen only in the proximal airways, thereby stimulating an immediate irritant effect. With cold air hyperventilation, hyperosmolality may be seen throughout the respiratory mucosa causing release of mediators and hence a delayed response in bronchospasm.²⁰

In summary, we have shown that a limited rise in the air temperature is not detrimental to persons with asthma when the water content is held equivalent to fully saturated body conditions. Moreover, we speculate that a water content of less than 44 mg H_2O per liter would be optimal. Because of its short-lived time course and disproportionate impact on the SG_{aw} , the detrimental effect of brief exposures to air supersaturated relative to the body temperature seems irritant in nature. Such irritation, however, could act as the trigger for a bronchospastic episode. The effect of a more prolonged exposure is currently unknown. Based on the data presented in this report, we recommend that inhaled water concentration not exceeding 44 mg H_2O per liter be used in patients with asthma.

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Spinal Headache

SPINAL ANESTHESIA CAN CAUSE HEADACHES. I think we should look a little bit at the characteristics of those headaches. First of all, they are due to decreased intracranial pressure due to loss of fluid from the subarachnoid space. What happens then is that when a patient assumes an erect position, the brain no longer has its normal buoyancy and tends, with gravity, to be pulled down, putting pressure on the meninges and causing a headache. Lie flat and the headache will go away. Usually it's very characteristic in that it comes on with sitting up and it goes away with lying down. It can be a frontal headache, it can be an occipital headache, it can be a nuchal headache. And especially, if your patient has a nuchal headache with rigidity, you're going to start being concerned, as you normally would, with meningitis. Then you have a differential diagnosis that you have to deal with because it would be reasonable to think the patient might have meningitis: you just put a foreign body in their subarachnoid space. It doesn't happen very often—it's very rare these days with spinal anesthesia—but it leaves us something to think about. Usually, these headaches have relatively immediate onsets, but onset can be up to six days postoperatively. The headaches have, usually, self-limiting courses—3 to 4 days—but they may go up to 2 weeks. Some have been reported to last for months.

—JOSEPH L. SELTZER, MD

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